PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference DPH 067-PCT/3	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/IB2004/001334	International filing date *(day/month/year)* 30.04.2004	Priority date *(day/month/year)* 30.04.2003
International Patent Classification (IPC) or national classification and IPC A61K38/09, A61K31/565, A61K9/16, A61P13/08, A61P35/00		
Applicant DEBIOPHARM S.A. et al.		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 8 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 7 sheets, as follows:
      ☒ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☒	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
28.02.2005	02.08.2005
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Veronese, A Telephone No. +49 89 2399-7824

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/IB2004/001334

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages

1-21 as originally filed

Claims, Numbers

1-25 received on 26.05.2005 with letter of 26.05.2005

Drawings, Sheets

1-3 as originally filed

☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 9-17(IA)

because:

☒ the said international application, or the said claims Nos. 9-17(IA) relate to the following subject matter which does not require an international preliminary examination (specify):

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the said claims Nos. 9-17(IA)

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	7-25
	No:	Claims	1-6
Inventive step (IS)	Yes:	Claims	7-8,10-25
	No:	Claims	1-6,9
Industrial applicability (IA)	Yes:	Claims	1-8,18-25
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

1. Re Item III.

Claims 9-17 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT). The other claims are considered industrially applicable.

2. Re Item V.

The following document have been cited in the search report. Where reference is made to them, the following numbering is used; unless otherwise indicated, reference is made to the relevant passages emphasized in the Search Report:

D1: US-A-5 340 584 (PIKE MALCOLM C ET AL) 23 August 1994 (1994-08-23)
D2: WO 94/26207 A (UNIVERSITY OF SOUTHERN CALIFORNIA), 1994-11-24
D3: US 2002/065260 A1 (NEUWINGER JOACHIM ET AL), 2002-05-30
D4: US-A-5 134 122 (ORSOLINI), 1992-07-28

The following document has now been added by the International Preliminary Examination Authority:

D5: Parenteral estrogen versus combined androgen deprivation in the treatment of metastatic prostatic cancer -- Scandinavian Prostatic Cancer Group (SPCG) Study No. 5. Scandinavian journal of urology and nephrology. 2002 VOL. 36(6) Page 405 - 413

2.1 Novelty Art.33(2) PCT

The applicant has amended the claims and incorporated the subject matter of original claim 3 in claim 1. The wording "comprising" in claims 1 and 3 has also been amended to "consist of". These amendments distinguish the compositions defined in independent claims 1 and 3 from the compositions of D1 which also comprise progesterone. These amendments however do not render these claims novel over D2.

D2 discloses pharmaceutical compositions comprising a slow release formulation of GnRH and a slow release formulation of an estrogen. The release time may extend from a minimum of at least one month to about six months (see D2 page 7, line 24-30). The GnRH is released at a rate which seems suitable to cause chemical castration (D2 page 9, line 1 and example 1).

Since the estrogen is present in the composition to limit the side effects produced by the GnRH, and in particular the loss of mineral density (see D2, page 15, line 16-27), the amount of estrogen which is released also appears to fall into the amount claimed in claim 1.

Furthermore, D2 examples 1 and 2 disclose examples of compositions comprising busereline (a preferred GNRH agonist in the present application) and estradiol (a preferred estrogen according in the present application). These active compounds are incorporated in the same lactide-glycolide microspheres (see D2, example 1), which according to the present application (page 11, lines 11-25) provide the desired release profiles.
D2 only discloses the plasmatic concentration provided by these compositions, and does not refer to their release profiles. However, considering the way these compositions were prepared, and the plasmatic concentrations which were obtained, it is reasonable to assume that these compositions fall among the claimed ones.
In the absence of a evidence that this is not the case claims 1-6 may not be considered new. The applicant has the burden of proof to demonstrate the contrary, but he has not discharged this burden yet.
Note: Even if the intended use of the compositions disclosed in D2 (treatment of gynaecological disorders) is different from the one for which the composition of the present application is meant (treatment of prostate cancer), such different use does not confer novelty to claims which are directed to pharmaceutical compositions as such.
Claims 7 and 8 (limited to tryptorelin) appear to be new over D1 and D2.

2.2 Inventive step (Art.33(3) PCT)

The problem underlying the present application is the provision of a pharmaceutical composition for the treatment of prostatic cancer which does not produce the typical side effects associated with GNRH therapy (bone loss and hot flashes in particular). According to the inventors, "the gold treatment" of prostatic cancer involves the use of GnRH agonists, but this treatment is accompanied by a number of side effects. To overcome these side effects, the inventors propose the administration (separately or in a single compositions) of:

- a sustained release formulation of a GnRH composition, during a period of at least one month, at a rate sufficient to maintain chemical castration and,
- a sustained release formulation of an estrogenic composition capable to maintain a serum level sufficient to reduce the side effects caused by the GnRH administration.

2.2a Claim 9 (not limited to a specific low amount of estrogen).

D3 relates to the use of GNRH for the treatment of prostatic cancer. D3 in fact relates to the treatment of diseases which can be treated by the administration of GNRH compositions, and prostatic cancer is clearly mentioned among these conditions (see "GNRH therapy", and "GNRH analogs" in paragraph 5; and see page 1, column 1, paragraph 6 and page 1, column 2, paragraph 11: " prostate carcinoma"). The problem underlying D3 is the reduction of the side effects produced by the administration of GNRH. As a solution, D3 proposes the administration of slow release GnRH formulations (for 1 month administration, see par. 55) in combination with certain estrogenic derivatives which are administered to reduce the side effects caused by the GnRH (hot flashes for example).
The main difference between claim 9 and **D3** is that the estrogen is administered in slow release form. It does however not appear that this difference produces any new special technical effect over the prior art.
Furthermore, controlled release forms of estrogens (estradiol) have already been used to treat of prostatic cancer (see **D5**). It would therefore be obvious to administer known controlled release compositions comprising estrogens and GNRH to treat prostate cancer. For this reason, the subject matter of claim 9 does not involve an inventive step over the prior art in the sense of Art.33(3) PCT.

2.2b Claims 10, 11, 18, 19 (limited to a specific low amount of estrogen) and the dependent claims (as long as they depend from claims 10, 11, 18, 19).

The subject matter of independent claims 10, 11,18,19 is characterized in that a low dosage of estradiol is administered in a controlled release formulation (dosages releasing 10-100 micrograms of estradiol equivalent per day which produce plasmatic concentrations up to 50 pg /ml).
From the prior art (D3 and D5) the skilled person would not have expected such low

concentrations of estrogen to be effective. D3 discloses the administration of 1-2 mg of estrogen in immediate release form (suppository, see par 55, "methods") and D5 teaches the administration of estradiol in controlled release form but in very high amounts (240 mg estradiol every two weeks).
For this reason, the subject matter of the claims directed to controlled release formulations releasing low amounts of estrogens are considered to involve an inventive step over the prior art.

2.3 Industrial Applicability

For the assessment of the present claims 9-17 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

3. Re Item VIII.

It is not clear whether independent claims 18 and 19 cover the same subject matter. In one case the claim defines the amount of estradiol which is released per day and in the other case defines the plasmatic concentration of estradiol which is produced by such composition.
Also, the definition of a composition by reference to the plasmatic concentration which such composition has to produce is considered unclear, since the determination of an "in vivo" plasmatic concentration causes an undue burthen on the skilled person interested to determine the scope of protection of the claim.

Claims

1. A composition consisting of :

a first sustained release formulation of a gonadotropin hormone releasing hormone composition capable of releasing the gonadotropin hormone releasing hormone composition during a period of at least about one month at a rate sufficient to induce and maintain chemical castration of a male patient, and

a second sustained release formulation of an estrogenic composition capable of maintaining for said period a serum level sufficient to reduce the enhanced loss of bone mineral density or the hot flashes that are normally caused by the administration of a gonadotropin hormone releasing hormone composition that chemically castrates a male patient,

characterised in that said second sustained release formulation releases an estrogenic composition under a profile comprising at least a first initial phase and a second phase, the release of the estrogenic composition in the course of said second phase being at a rate between about 10 and 100 µg of estradiol equivalent per day, the release of the estrogenic composition in the course of said first initial phase never exceeding 5 times the daily release of the estrogenic composition occurring during said second phase.

2. The composition according to claim 1, characterised in that said first sustained release formulation of a gonadotropin hormone releasing hormone composition is capable of releasing the gonadotropin hormone releasing hormone composition at a rate between about 10 and about 1,000 µg per day.

3. A composition consisting:

a first sustained release formulation of a gonadotropin hormone releasing hormone composition capable of releasing the gonadotropin hormone releasing hormone composition for a period of at least about one month at an average rate between about 10 and 1,000 µg per day, and

a second sustained release formulation of an estrogenic composition capable of releasing the estrogenic composition under a profile comprising at least a first initial phase and a second phase, the release of the estrogenic composition in the course of said second phase being at a rate between about 10 and 100 µg of estradiol equivalent per day, the release of the estrogenic composition in the course of said first initial phase never exceeding 5 times the upper daily release of the estrogenic composition occurring during said second phase.

4. The composition according to any of the preceding claims, characterised in that the gonadotropin hormone releasing hormone composition is selected from the group consisting of gonadotropin hormone releasing hormone, agonists of gonadotropin hormone releasing hormone, antagonists of gonadotropin hormone releasing hormone and mixtures thereof.

5. The composition according to claims 1, 2, or 3, characterised in that the gonadotropin hormone releasing hormone composition is a gonadotropin hormone releasing hormone agonist selected from the group consisting of leuprorelin, goserelin, triptorelin, buserelin, nafarelin, deslorelin, histerelin, gonadorelin, and salts and mixtures thereof.

6. The composition according to claims 1, 2, or 3, characterised in that the estrogenic composition is selected from the group consisting of chlorotrianisene, dienestrol, diethylstilbestrol, diethylstilbestrol dipropionate, diethylstilbestrol monobenzyl ether, equilelinin, equilelinin sulfate, estetrol, estradiol, (3α,17β)-estr-4-ene-3,17-diol, estriol, estriol hemisuccinate, estrone, estrone sulfate monosodique, estrone potassium sulfate, ethinylestradiol, fosfestrol tetrasodique, hexestrol, hydroxyestrone diacetate, mestranol, pinestrol, piperazine estrone sulfate, promestriene, quinestrol, tamoxifen, toremifene, raloxifene, lasofoxifene and mixtures thereof.

7. The composition according to claims 1, 2, or 3, characterised in that the gonadotropin releasing hormone composition is triptorelin or a salt thereof and the estrogenic composition is estradiol.

8. The composition of claim 7, characterised in that triptorelin, or a triptorelin salt, is released at a rate of about 100 µg per day and estradiol is released at a rate between about 25 and 50 µg per day.

9. A method for the treatment of prostate cancer comprising:
Administering to a patient suffering from prostate cancer a sustained release formulation of a gonadotropin hormone releasing hormone composition capable of releasing the gonadotropin hormone releasing hormone composition for a period of at least about one month at a rate sufficient to induce and maintain chemical castration of the patient, and

Simultaneously administering to the patient a sustained release formulation of an estrogenic composition capable of maintaining for said period a serum level sufficient to reduce the enhanced loss of bone mineral density or the hot flashes that are normally caused by the administration of a gonadotropin hormone releasing hormone composition that chemically castrates a male patient.

10. A method for the treatment of prostate cancer comprising:

Administering to a patient suffering from prostate cancer a sustained release formulation of a gonadotropin hormone releasing hormone composition capable of releasing the gonadotropin hormone releasing hormone composition for a period of at least about one month at an average rate between about 10 and 1,000 µg per day, and

Simultaneously administering to the patient a sustained release formulation of an estrogenic composition under a profile comprising at least a first initial phase and a second phase, the release of the estrogenic composition in the course of said second phase being at a rate between about 10 and 100 µg of estradiol equivalent per day, the release of the estrogenic composition in the course of said first initial phase never exceeding 5 times the upper daily release of the estrogenic composition occurring during said second phase.

11. A method for the treatment of prostate cancer comprising:

Administering to a patient suffering from prostate cancer a sustained release formulation of a gonadotropin hormone releasing hormone composition capable of releasing the gonadotropin hormone releasing hormone composition for a period of at least about one month at an average rate between about 10 and 1,000 µg per day, and

Simultaneously administering to the patient a sustained release formulation of an estrogenic composition under a profile comprising at least a first initial phase and a second phase, the release of the estrogenic composition in the course of said second phase being at a rate between about 10 and 100 µg of estradiol equivalent per day, the release of the estrogenic composition in the course of said first initial phase never exceeding 5 times the upper daily release of the estrogenic composition occurring during said second phase.

12. A method as in claims 9, 10 or 11, wherein the gonadotropin hormone releasing hormone composition is selected from the group consisting of gonadotropin hormone releasing hormone, agonists of gonadotropin hormone releasing hormone, antagonists of gonadotropin hormone releasing hormone and mixtures thereof.

13. A method as in claims 9, 10 or 11, wherein the gonadotropin hormone releasing hormone composition is a gonadotropin hormone releasing hormone agonist selected from the group consisting leuprorelin, goserelin, triptorelin, buserelin, nafarelin, deslorelin, histerelin, gonadorelin, and salts and mixtures thereof.

14. A method as in claims 9, 10 or 11, wherein the estrogenic composition is selected from the group consisting of chlorotrianisene, dienestrol, diethylstilbestrol, diethylstilbestrol dipropionate, diethylstilbestrol monobenzyl ether, equilelinin, equilelinin sulfate, estetrol, estradiol, (3α,17β)-estr-4-ene-3,17-diol, estriol, estriol hemisuccinate, estrone, estrone sulfate monosodique, estrone potassium sulfate, ethinylestradiol, fosfestrol tetrasodique, hexestrol,

hydroxyestrone diacetate, mestranol, pinestrol, piperazine estrone sulfate, promestriene, quinestrol, tamoxifen, toremifene, raloxifene, lasofoxifene and mixtures thereof.

15. A method as in claims 9, 10 or 11, wherein the gonadotropin releasing hormone composition is triptorelin or a salt thereof and the estrogenic composition is estradiol.

16. A method according to claim 15, wherein triptorelin, or a triptorelin salt, is released at a rate of about 100 µg per day and estradiol is released at a rate between about 25 and 50 µg per day.

17. A method as in claims 9, 10 or 11, wherein the composition is administered by a subcutaneous, intramuscular, or transdermal route.

18. Use of a composition comprising:

a first sustained release formulation of a gonadotropin hormone releasing hormone composition capable of releasing the gonadotropin hormone releasing hormone composition during a period of at least about one month at a rate sufficient to induce and maintain chemical castration of a male patient, and

a second sustained release formulation of an estrogenic composition capable of maintaining for said period a serum level sufficient to reduce the enhanced loss of bone mineral density or the hot flashes that are normally caused by the administration of a gonadotropin hormone releasing hormone composition that chemically castrates a male patient, said serum level in estradiol equivalent being less than about 50 pg/ml.

19. Use of a composition comprising:

a first sustained release formulation of a gonadotropin hormone releasing hormone composition capable of releasing the gonadotropin hormone releasing

hormone composition for a period of at least about one month at an average rate between about 10 and 1,000 µg per day, and

a second sustained release formulation of an estrogenic composition capable of releasing the estrogenic composition under a profile comprising at least a first initial phase and a second phase, the release of the estrogenic composition in the course of said second phase being at a rate between about 10 and 100 µg of estradiol equivalent per day, the release of the estrogenic composition in the course of said first initial phase never exceeding 5 times the upper daily release of the estrogenic composition occurring during said second phase,

for the preparation of a medicament for treatment of prostate cancer in a patient suffering from prostate cancer, said first sustained release formulation and said second sustained release formulation being simultaneously administrated to said patient.

20. The use according to any of the claims 18 or 19, characterised in that the gonadotropin hormone releasing hormone composition is selected from the group consisting of gonadotropin hormone releasing hormone, agonists of gonadotropin hormone releasing hormone, antagonists of gonadotropin hormone releasing hormone and mixtures thereof.

21. The use according to any of the claims 18 or 19, characterised in that the gonadotropin hormone releasing hormone composition is a gonadotropin hormone releasing hormone agonist selected from the group consisting leuprorelin, goserelin, triptorelin, buserelin, nafarelin, deslorelin, histerelin, gonadorelin, and salts and mixtures thereof.

22. The use according to any of the claims 18 or 19, characterised in that the estrogenic composition is selected from the group consisting of chlorotrianisene, dienestrol, diethylstilbestrol, diethylstilbestrol dipropionate, diethylstilbestrol monobenzyl ether, equilelinin, equilelinin sulfate, estetrol, estradiol, (3α,17β)-estr-4-ene-3,17-diol, estriol, estriol hemisuccinate, estrone, estrone sulfate monosodique, estrone potassium sulfate, ethinylestradiol,

fosfestrol tetrasodique, hexestrol, hydroxyestrone diacetate, mestranol, pinestrol, piperazine estrone sulfate, promestriene, quinestrol, tamoxifen, toremifene, raloxifene, lasofoxifene and mixtures thereof.

23. The use according to any of the claims 18 or 19, wherein the gonadotropin releasing hormone composition is triptorelin or a salt thereof and the estrogenic composition is estradiol.

24. The use according to claim 23, wherein triptorelin, or a triptorelin salt, is released at a rate of about 100 µg per day and estradiol is released at a rate between about 25 and 50 µg per day.

25. The use according to any of the claims 18 or 19, wherein the composition is administered by a subcutaneous, intramuscular, or transdermal route.